CURRENT TRENDS IN INITIAL MANAGEMENT OF HYPOPHARYNGEAL CANCER: THE DECLINING USE OF OPEN SURGERY

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Abstract: Squamous cell carcinoma of the hypopharynx represents a distinct clinical entity. Most patients present with significant comorbidities and advanced-stage disease. The overall survival is relatively poor because of high rates of regional and distant metastasis at presentation or early in the course of the disease. A multidisciplinary approach is crucial in the overall management of these patients to achieve the best results and maintain or improve functional results. Traditionally, operable hypopharyngeal cancer has been treated by total (occasionally partial) laryngectomy and partial or circumferential pharyngectomy, followed by reconstruction and postoperative radiotherapy in most cases.

Efforts to preserve speech and swallowing function in the surgical treatment of hypopharyngeal (and laryngeal) cancer have resulted in a declining use of total laryngopharyngectomy and improved reconstructive efforts, including microvascular free tissue transfer. There are many surgical, as well as nonsurgical, options available for organ and function preservation, which report equally effective tumor control and survival. The selection of appropriate treatment is of crucial importance in the achievement of optimal results for these patients. In this article, several aspects of surgical and nonsurgical approaches in the treatment of hypopharyngeal cancer are discussed. Future studies must be carefully designed within clearly defined populations and use uniform terminology and standardized functional assessment and declare appropriate patient or disease endpoints. These studies should focus on improvement of resultsx, without increasing patient morbidity. In this respect, technical improvements in radiotherapy such as intensity-modulated radiotherapy, advances in supportive care, and incorporation of newer systemic agents such as targeted therapy, are relevant developments. © 2010 Wiley Periodicals, Inc. *Head Neck* **34:** 270–281, 2012

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Squamous cell carcinoma of the hypopharynx is less prevalent than at most other major sites of the head and neck, such as the oral cavity, larynx and oropharynx, and accounts for approximately 3% to 5% of all head and neck squamous cell carcinomas (HNSCC).[1,2] Tumors arising in the hypopharynx have their own

specific and unique characteristics and considerations regarding treatment. A high proportion of the patients are heavy drinkers of alcohol and have additional significant comorbidities.[1] Most patients when diagnosed have advanced-stage disease. Approximately 70% to 85% of the patients reported in large series have stage III or IV disease at presentation, and the 5-year overall survival rate is reported to be around 15% to 45%.[1–7] The anatomic proximity of the larynx, advanced stage of disease at presentation, and higher rates of regional and distant metastasis portend a worse prognosis compared with other head and neck cancer sites and are factors that require consideration when making treatment decisions.

As reviewed by Gourin and Terris,[8] the important factors in this dismal prognosis in patients who present with a hypopharyngeal cancer are the high rates of regional and distant metastasis. Approximately 60% to 80% of the patients have clinically apparent tumor involved regional lymph nodes, and contralateral occult nodal metastases are present in nearly 40% of cases.[9] The number of patients with development of distant metastasis, reported to be between 10% and 30% or even higher, is an even more important prognostic factor. Distant metastatic spread has been reported to occur in up to 60% of hypopharyngeal cancer cases,[10] either at presentation or during follow-up, and is more frequent compared with other HNSCCs. Predominant sites of systemic dissemination are the lung, mediastinal lymph nodes, liver, and bone. These patients are usually treated in the context of various study protocols in which median survival is typically less than a year.

In an epidemiologic study of a series of 595 patients with hypopharyngeal cancer in Ontario, Canada, Hall et al[1] reported that almost 50% of the patients had recurrences, most within 12 months after completion of treatment. Fifty percent of these recurrences involved distant metastasis. Multicentricity is also a common pathologic feature of hypopharyngeal cancers, as well as considerable submucosal spread, and, when treated surgically, the margins of excision frequently demonstrate the presence of tumor. Airway and nutritional issues are difficult problems in patients presenting with advanced hypopharyngeal cancer. Soft tissue extension of the disease involving the constrictor musculature, the soft tissues of the neck, and the parapharyngeal space is quite common.

TREATMENT CHOICES

Traditionally, laryngopharyngectomy with reconstruction of the pharynx has been the preferred initial treatment modality for hypopharyngeal cancers. In an attempt to limit the morbidity of surgical therapy, nonsurgical treatments have gained popularity. However, treatment with radiotherapy alone is reported to have a worse prognosis compared with combined treatment with surgery and radiotherapy, particularly in stage IV disease.[3,6,11] The addition of chemotherapy to primary radiotherapy protocols results in outcomes comparable to surgery and postoperative radiotherapy, but with the advantage of larynx preservation in a large number of cases.[12] However, unlike advanced laryngeal cancers, the question of organ preservation in hypopharyngeal cancer has not been thoroughly evaluated, precluding firm conclusions as to which is the optimal treatment.[13,14]

The terms "organ preservation" and "larynx preservation" in particular are frequently unclearly defined or interpreted. In fact, the terms only mean that the organ has been left anatomically intact and free from surgical intervention but are not indicative of function. Therefore, organ preservation should not be confused with function preservation. With regard to hypopharyngeal cancer, function includes both voice and swallowing and, in a broader sense, quality of life. Function may even be better preserved after removal of the organ, permitting aspiration free deglutition and prosthetic voice than by leaving intact a functionless larynx. Formal studies on this subject are lacking, but physicians involved with this problem are well aware of its existence. In many cases it may be more important to the patient to preserve or restore function rather than to simply preserve an intact but poorly functioning larynx. Stimulated by past experiences and observations, a multidisciplinary international group of experts recently evaluated results from pertinent phase III clinical trials and meta-analyses with the aim of developing guidelines for the conduct of contemporary phase III larynx preservation trials. Emphasis was made in these guidelines on refining the definition of a functional larynx within a context of organ preservation treatment strategies and to determine the best methods for assessment of function.[15]

Moreover, larynx preservation as a treatment strategy, although intended to preserve the organ, includes the option of surgical salvage in cases of persistent or recurrent disease in an effort to obtain optimal patient survival rates comparable to those of primary surgery followed by postoperative (chemo)radiotherapy. Thus organ preserving strategies as a concept for curative treatment are not exclusively nonsurgical.

Neck dissection or irradiation is usually part of the initial treatment of hypopharyngeal cancer because of the high rate of clinically apparent, as well as occult, nodal metastasis. The primary echelon drainage is to the jugular chain (levels II to IV), but the retropharyngeal and level VI nodes are all at risk.[16] In elective treatment of occult regional metastasis, the high incidence of retropharyngeal and paratracheal metastasis,[17] as well as the high rate of contralateral metastasis,[9] should be considered. The low incidence or even absence of nodal metastasis found in sublevel IIB and level I, in particular, may justify the preservation of these levels in the elective treatment of the N0 neck in patients with hypopharyngeal cancer.[18–20] The several treatment options for hypopharyngeal carcinoma will be discussed.

PRIMARY SURGERY

For decades, the treatment protocol that afforded the best oncologic outcomes for hypopharyngeal cancer consisted of radical surgery and postoperative radiotherapy. More recently, the role of initial surgery has been diminished in favor of nonsurgical treatment regimens of radiotherapy combined with platinum-based chemotherapy. However, in early-stage disease, surgery is still a treatment option. Also, in cases of extensive disease, when most patients will already have seriously impaired laryngeal and hypopharyngeal function, surgery with adequate reconstruction, followed by radiotherapy, may have both the best functional and oncologic outcomes.

Three surgical options are available for treatment of hypopharyngeal cancer: "radical" open surgery [total laryngopharyngectomy (TLP) or total laryngectomy with partial pharyngectomy], partial open surgery (partial laryngectomy with pharyngectomy), and partial transoral (or minimally invasive) surgery.

Total Laryngopharyngectomy. Traditionally, lesions that involve more than two thirds of the circumference of the hypopharynx have been treated by radical surgery, consisting of total laryngectomy and circumferential pharyngectomy, including varying amounts of cervical or even thoracic esophagus, followed by radiotherapy in most cases. The 5-year disease-specific survival rate has been reported to be between 40% and 50%.[4,21,22] Postoperative chemoradiotherapy is reported to further improve tumor control.[23]

The resulting surgical pharyngoesophageal defects require reconstruction and institutional preferences often depend on factors such as the training specialty of the surgical team and the expertise of the available team.[24] Hypopharyngeal reconstruction has been a major challenge over the years. The deltopectoral flap was the only reconstructive approach before the pectoralis myocutaneous flap became available in the 1970s. The pectoralis myocutaneous flap is a reliable reconstructive method for lesions with minimal extension into the esophagus and has proved useful in severely depleted or elderly patients.[25,26] This flap, or other myocutaneous flaps are also useful as an onlay patch pharyngoplasty, when a partial pharyngeal defect has been created. Gastric "pull-up" or transposition is generally recommended for tumors that have extended as far as the middle third of the esophagus or where the resected lower margin is deeply placed within the mediastinum, making any safe surgical repair difficult. However, there is a considerable learning curve in performing gastric transposition, which requires careful coordination between the head and neck and thoracic surgeons. More recently the introduction of microvascular and free flap reconstruction has revolutionized the surgical approaches and functional results in hypopharyngeal cancer, both for "patch" or circumferential reconstruction. Microvascular flaps commonly used are jejunum, radial forearm free flap, or anterolateral thigh flap.

Fasciocutaneous free flap, anterolateral thigh flap, and radial forearm free flap reconstructions are currently being used more frequently than the intestinal flaps because of reliability, technical accessibility, and popularity with surgeons.[27] Functional outcomes have been reported to be better with modern fasciocutaneous free flap reconstruction compared with the traditional jejunal flap, and the donor site morbidity is reported as minimal.[27,28] However, the morbidity after flap reconstruction is reported to be considerable. In a large surgical series of 153 patients (involving 85 partial and 68 circumferential pharyngectomies, and about 50% of patients had surgery after previous radiotherapy), fistulas and wound complications were seen in 33% and 25% of cases, respectively. The late complication and stricture rates were 26% and 15%, respectively, and 16% of patients required permanent feeding through a gastrostomy tube. It was also reported that only 44% of patients had surgical voice restoration with a tracheoesophageal puncture.[29]

Partial Surgery. More conservative surgical procedures have been used for the treatment of hypopharyngeal cancer. As surgical organ preserving procedures, endoscopic (laser) microsurgery, endoscopic robotic surgery, lateral pharyngectomy, and hemilaryngopharyngectomy are possible endoscopic and external approaches described. However, these procedures can only be considered in selected cases, usually early (T-stage) cancer, and the choice of such limited surgical procedures must recognize that hypopharyngeal cancers have a high predilection to extensive submucosal tumor spread.

Open Procedures. For tumors arising in the upper part of the pyriform sinus or the aryepiglottic fold, a supraglottic hemilaryngopharyngectomy can be used. Although the technique had been used for many decades, one of the first large series of supraglottic laryngectomy and partial pharyngectomy for cancers of the pyriform sinus was published in 1980 by Ogura et al.[30] In this series of 175 patients treated for carcinoma of the pyriform sinus; 85 underwent partial laryngopharyngectomy (PLP); 57, TLP; and 33, palliative radiation. The actuarial 3-year survival rate was 59% for the PLP-treated group, 36% for the TLP-treated group, and 11% for the palliation group. The better outcome for the PLP-treated group as compared with the TLP-treated group should be attributed to selection of lower-staged tumors eligible for this treatment.

In 1993, Laccourreye et al[31] reported on a series of patients treated between 1964 to 1985 with a supracricoid hemilaryngopharyngectomy (SCHLP) performed on selected pyriform sinus carcinomas classified as T2. Tumors with invasion of the apex of the pyriform sinus, of the postcricoid region, of the

posterior pharyngeal wall, or with fixation of the true vocal cord were excluded from this study. This technique was aimed at preserving physiologic phonation, respiration, and swallowing while achieving the same local control rate as a pharyngolaryngectomy. Patients were followed up for at least 6 years or until death. Five-year actuarial locoregional control was reported at 95% with a 5-year disease-specific survival rate of 56%. The 5-year actuarial local recurrence rate was 3.4%. The author considered the SCHLP technique to be a safe method of voice preservation in selected cases of pyriform sinus carcinoma. In 2005, the same group reported on SCHLP performed on 147 patients over a 19-year period. All patients had previously untreated invasive squamous cell carcinoma of the pyriform sinus.[32,33] Before surgery, almost all (97%) of the patients had a cisplatin-based induction chemotherapy regimen. A complete clinical response and a complete histopathologic regression were noted in 22% and 17% of patients, respectively. Postoperative radiotherapy was given in approximately 50% of patients. The 5-year actuarial local control estimate was 90%, and the overall laryngeal preservation rate was 91%. On regression analysis, positive resection margins and invasion of the apex of the pyriform sinus were identified as adverse factors for predicting local recurrence.

In another series of 48 selected cases treated by the same technique of induction chemotherapy followed by surgery, all T1 or T2 and arising at the pyriform sinus or aryepiglottic fold, the 5-year survival rate was 47%.[34] All patients achieved deglutition without aspiration by the end of the first postoperative month. All but 5 patients received postoperative radiotherapy. Postoperative death or prior radiotherapy was the reason for not undergoing radiotherapy. All patients had ipsilateral (radical) neck dissection. Neck recurrence was 15%, and local recurrence was 2%. Other series report similar results with 5-year overall survival rates around 50%, and disease-specific survival rates of 60% to 65% in these selected cases, mostly treated with postoperative radiotherapy and a larynx preservation rate in the order of 80%.[35,36]

Transoral (Minimally Invasive) Procedures. Transoral laser surgery (TOLS) was initially employed for the resection of laryngeal cancers,[37,38] but its use was later extended to hypopharyngeal cancer.[39,40] Zeitels et al[39] was one of the first to publish on TOLS for supraglottic and hypopharyngeal cancer. He reported on 45 cases, of which 22, mostly classified T1, had TOLS only, and 23 with locally more extensive tumors, but all N0, received additional radiotherapy locally and to the neck. Seven of the 23 cases had positive margins, and 5 (26%) of these failed locoregionally.

Steiner et al[41] retrospectively reviewed 129 previously untreated patients with squamous cell carcinoma of the pyriform sinus treated by TOLS. Of these, 24 tumors were staged as pT1, 74 as pT2, 17 as pT3, and 14 as pT4. Overall, 68% of these patients had nodal metastases. Of all cases, treatment consisted of TOLS and neck dissection surgery alone in 42%, and 58% also underwent postoperative radiotherapy. The 5-year overall survival rate was 71% for patients with stage I and II disease, and 47% for patients with stage III and IV disease. The reported 5-year recurrence-free survival rate for stage I/II and stage III/IV disease was 95% and 69%, respectively.

Rudert and Höft[42] reported a 100% larynx and pharynx organ preservation rate with a 5-year overall survival rate of 48% and disease-specific survival rate of 58% in a series of 29 predominantly T1 and T2 hypopharyngeal tumors. All but 3 patients underwent postoperative radiotherapy, and all but 4 underwent neck dissection. In this selected group, no symptomatic alteration in swallowing was reported, and the technique was considered suitable for cancers of the posterior hypopharyngeal wall, in particular.

In a series by Vilaseca et al[43] of 28 patients treated with TOLS, 21% (6 patients) had stage II disease, 29 % (8 patients) stage III, and 50% (14 patients) stage IV. All patients underwent unilateral or bilateral neck dissection. Of these patients, 43% had radiotherapy to the neck, and 14% had radiotherapy locoregionally. Of the 14 patients alive and without disease in the follow-up period, 11 (79%) had their larynx functionally preserved, but 3 (21%) were gastrostomy dependent.

Kutter et al[44] analyzed 55 consecutive patients with pharyngeal or pharyngolaryngeal squamous cell carcinoma (24 = T1, 28 = T2, 3 = T3) treated with TOLS. Neck dissection was performed in 43 patients. In this group, the 2-year overall survival rate was 78%, and local control was 90%.

Martin et al[45] reported on a larger series of 172 patients with hypopharyngeal cancer treated from 1986 to 2003 with TOLS, of whom 15% had stage I and II disease and 85% had stage III and IV disease. Of these tumors, 87% originated in the pyriform sinus. The 5-year overall survival rate was 68% for stage I and II, 64% for stage III, and 41% for stage IV. In this series 52% underwent postoperative chemoradiation, and 91% underwent unilateral or bilateral neck dissection. Only 1 patient required laryngectomy for functional reasons, and 6 patients had permanent gastrostomy tubes.

In summary, the oncologic results of TOLS appear comparable with open approaches, with a 5-year overall survival rate of around 50% to 70% in stage I and II disease and 40% to 50% in stage III and IV disease. The disease-specific survival rate with TOLS is on the order of 60% and is associated with high rates of larynx preservation in these selected cases. However, most patients continue to require postoperative radiotherapy.

Transoral robotic surgery is a minimally invasive surgical technique with the carbon dioxide laser and is currently used for treatment in selected cases and

selected sites of head and neck cancers. However, the hypopharynx is not optimally accessible for this technique. Published series contain very small numbers of hypopharyngeal cancer cases and mention the aryepiglottic fold or posterior wall as primary tumor sites suitable for this approach.[46–48]

PRIMARY CHEMOTHERAPY OR BIO-RADIOTHERAPY

As mentioned before, the results of primary definitive radiotherapy followed by salvage surgery when indicated, compared to initial surgery with postoperative radiotherapy, are reported to be inferior in terms of survival, particularly for advanced stage tumors.[13,49] However, in early-stage hypopharyngeal cancer similar results can be obtained with definitive radiotherapy regimens[50] with overall survival and disease-specific survival rates reported to be comparable to those after total laryngectomy or larynx-conserving surgery.[51–53]

In the 1990s, the first reports on larynx preservation strategies became available. In 1994, the initial report of a phase III study conducted by the Department of Veterans Affairs Laryngeal Cancer Study Group was published.[54] Patients with stage III-IV laryngeal cancer were randomly assigned to receive 2 cycles of induction chemotherapy with cisplatin and 5-fluorouracil. Those responding (partial or complete) received a third cycle, followed by radiotherapy. Patients not responding clinically to the initial cycles of chemotherapy were offered a total laryngectomy. Survival rates at 2 years appeared to be comparable to surgery followed by radiotherapy (68% for both treatment groups), and the larynx was preserved in approximately two thirds of the cases. However, patterns of first recurrence differed significantly between the 2 arms, with local recurrences occurring more frequently in the chemotherapy-radiotherapy arm, whereas distant metastases were more common in the surgically treated patients. Overall, there were no significant differences in eventual rate of distant metastases or in cause of death. However, none of these patients were treated for hypopharyngeal cancer.

One of the few randomized phase III trials on hypopharyngeal cancer specifically comparing the results of initial surgical versus nonsurgical treatment was conducted by the European Organization for Research and Treatment of Cancer (EORTC).[12] Eligible patients with hypopharyngeal or epilaryngeal cancer were randomized between induction PF followed by definitive radiotherapy versus surgery with postoperative radiotherapy. No differences were found in local or regional recurrence and disease-free survival rates at 5 years. The disease-free survival rate at 5 years was 25% in the induction chemotherapy arm and 27% in the immediate surgery arm. In this study, the survival rate with a functional larynx in the chemoradiation group after 5 year was 35%, which is similar to other studies.[8] This larynx preservation rate appears to be inferior compared with that for laryngeal cancer, but it should be emphasized that the 2 endpoints are difficult to compare. First, in the Veterans Affairs Laryngeal Cancer Study Group trial, the larynx preservation rate was reported at 2 years instead of 5 years as in the EORTC study. Moreover, in the EORTC study, the endpoint was referred to as survival with a functional larynx (ie, without local disease, tracheotomy, feeding tube, or gastrostomy).

Recently, the EORTC reported on their second larynx preservation study.[55] In this study, patients with resectable carcinoma of the larynx (T3-T4, N0-N2) or hypopharynx (T2-T4, N0-N2), were randomly assigned to receive induction chemotherapy followed by radiotherapy in the responders, as described earlier, or an alternating chemoradiation regimen, including a total of 4 cycles of PF (in weeks 1, 4, 7, and 10) alternated with radiotherapy, 20 Gy during the three 2-week intervals between chemotherapy cycles (60 Gy total). The number of laryngeal and hypopharyngeal cancers was well balanced between the 2 arms. Again, the same primary endpoint was used: survival with a functional larynx. The 2 arms showed similar results, as they did with regard to overall survival, progression-free survival, and acute and late toxicity. It should be emphasized that in the alternating chemoradiation arm, the total dose of radiation was reduced to 60 Gy compared with 70 Gy in the sequential arm, and that the overall treatment time of radiation was prolonged as a result of the alternating schedule from 7 weeks to 8 weeks or more. Therefore, it cannot be concluded from this study that sequential chemoradiation provide similar results to conventional concomitant chemoradiation with 70 Gy of radiation with standard fractionation and 3 courses of cisplatin 100 mg/m^2 in weeks 1, 4, and 7.

In 2003, Forastiere et al[56] reported on the results of the RTOG 91-11, a phase III study in which patients with glottic and supraglottic tumors (T2–T4) were randomly assigned to receive induction PF followed by radiotherapy in responders, concomitant cisplatin-based chemoradiotherapy, or radiotherapy alone. Although overall survival rates were similar in all 3 treatment arms, the highest rate of larynx preservation was observed after concomitant chemoradiation (88% vs 75% in the induction chemotherapy arm vs 70% in the radiotherapy alone arm), which also resulted in superior locoregional control (78% vs 61% vs 56%). But again this trial included laryngeal and not hypopharyngeal cancer. A trial update in 2006 confirmed these results.[57] It should be noted that in the initial report, salvage total laryngectomy after these organ preservation treatment strategies was associated with acceptable morbidity rates and resulted in excellent locoregional control, although the survival rate at 2 years for patients requiring salvage total laryngectomy was lower than for patients remaining disease-free at the primary site.[58] However, on the basis of updated results, some concern was raised regarding the high mortality rate

from unknown causes noted during follow-up, which may have arisen from secondary aspiration, pneumonia, or other unrecognized sequelae of treatment.[59] Apart from larynx preservation, overall survival only shows modest differences at best between the different regimens for laryngeal cancer and do not seem to significantly differ from "traditional" surgery followed by radiotherapy in the treatment of head and neck cancer in general.[60]

In 2000, Pignon et al[61] published the results of individual patient data meta-analysis of 63 randomized trials on locoregional treatment (surgery or radiotherapy) with or without chemotherapy, performed between 1965 and 1993. The study involved 10,741 patients with nonmetastatic HNSCC (Meta-Analysis of Chemotherapy in Head and Neck Cancers). The investigators found an absolute survival benefit of 4% at 2 and 5 years in favor of the addition of chemotherapy. However, in the group of trials on concomitant chemoradiation, an 8% absolute benefit at 5 years in the experimental arm was highly significant. The authors concluded at that time that because the analysis showed only a small significant survival benefit in favor of chemotherapy and, in particular, because of the heterogeneity of the results, which required cautious interpretation, "the routine use of chemotherapy is debatable" and that "for larynx preservation, the non-significant negative effect of chemotherapy in the organ preservation strategy indicates that this procedure must remain investigational."

Since that time more studies have been conducted, and the results of the meta-analysis of the updated database of the Meta-Analysis of Chemotherapy in Head and Neck Cancers group with 87 trials conducted between 1965 and 2000, with a total of 16,486 patients, was published recently.[62] An absolute survival benefit for chemotherapy of 4.5% at 5 years confirmed previous results, as did the most pronounced benefit observed in concomitant trials (6.5% at 5 years). No survival advantage was shown for induction chemotherapy, although this should be interpreted with caution as taxane-based induction chemotherapy trials, which already proved to be superior to the reference PF combination, were not included in meta-analysis. This time the authors concluded that "the benefit of concomitant chemotherapy was confirmed," and results "should be useful to determine standard treatment in this disease." It should be noted that in the initial as in the updated results of the meta-analysis, the subset analysis did not reveal any difference between the different tumor sites. The beneficial effect of the addition of concomitant chemoradiation reference to radiotherapy alone was similar among patients with hypopharyngeal cancer to that observed among patients with other primary tumor sites.

Increasingly intensive treatment regimens have been investigated, not only of concomitant chemoradiotherapy protocols but also sequential approaches consisting of both induction chemotherapy followed by radiotherapy alone or concomitant chemoradiotherapy. The addition of taxanes to the platinum-based induction chemotherapy seems to further improve outcomes, especially for laryngeal preservation. In patients with advanced laryngeal and hypopharyngeal carcinomas, induction chemotherapy consisting of docetaxel, cisplatin, and 5-fluorouracil appeared to be superior to a regimen consisting of PF in terms of overall response rate (complete and partial responses, 80% vs 59%, $p = .002$). Larynx preservation could be achieved for a higher proportion of patients in the docetaxel-cisplatin-fluorouracil group compared with the cisplatin-fluorouracil group (at 3 years: 70% vs 57.5%, $p = .03$), but again without associated overall survival benefit (60% at 3 years in both arms).[63]

Posner et al[64] reported on a similar phase III trial of sequential therapy comparing docetaxel-cisplatin-fluorouracil against cisplatin-fluorouracil induction chemotherapy, followed by chemoradiotherapy with weekly carboplatin. In addition to patients with unresectable oral cavity, oropharyngeal, hypopharyngeal, or laryngeal cancer, patients considered to be candidates for organ preservation were also included (33% and 35% of patients in each arm of the trial). Laryngectomy-free survival was significantly greater with docetaxel-cisplatin-fluorouracil: at 3 years 52% vs 32%. Fewer patients treated with docetaxel-cisplatin-fluorouracil underwent surgery (22% vs 42%). In this study there was also a significant benefit regarding overall survival in favor of docetaxel-cisplatin-fluorouracil induction chemotherapy.

Another important aspect of nonsurgical approaches is their potential ability to counteract the development of distant metastases. Different patterns of recurrence with fewer initial distant metastases in the induction chemotherapy group compared to the surgery group were observed in The Department of Veterans Affairs' study,[54] which was confirmed by other authors.[65] This may be another argument in favor of inclusion of systemic agents in organ preservation treatment protocols. Whereas the concomitant use of irradiation and systemic therapeutics has been proven to successfully improve locoregional disease control and to a lesser extent also distant metastases-free survival,[62] the sequential chemoradiation strategies incorporating induction chemotherapy protocols are aimed at diminishing the incidence of distant failures. According to the results of a recent meta-analysis this seems to be the case.[62]

For those patients with M1 disease, prognosis is dismal. Although these patients in particular are directed to take part in experimental clinical protocols exploring new systemic drugs and their combinations, the median survival times are usually less than a year. The results of studies testing a new treatment paradigm combining immunotherapeutic and conventional chemotherapeutics look promising, although tumor sites other than the hypopharynx were included.[66]

It may be concluded from the data of these studies that intensifying treatment may increase the rate of larynx preservation but survival benefit has been reported less consistently.[59,67,68] In addition, interpretation of the (sometimes conflicting) results of chemoradiotherapy trials may be hampered by several factors. Studies often consist of populations with a different mix of both laryngeal and hypopharyngeal cancer and end-points are differently defined or chosen.[69]

TOXICITY OF CHEMORADIATION PROTOCOLS AND QUALITY OF LIFE

Besides other toxic effects, both acute and late (xerostomia, skin toxicity, cervical fibrosis and lymphedema, ototoxicity),[70,71] significant swallowing dysfunction is a common finding after intensive chemoradiotherapy. In patients with HNSCC, the rate of symptomatic strictures is estimated to be around 20%, with a hypopharyngeal primary site as a significant predictive factor.[72] Fixation of the vocal cord, in particular, seems to be a predictor of poor functional outcome,[73] and even total pharyngeal obstruction may occur.[74] Impaired swallowing function promotes aspiration, which may lead to pneumonia. Aspiration pneumonia may be an underdocumented and underreported complication of chemoradiotherapy for HNSCC. Future studies should examine whether routine posttherapy videofluoroscopy and swallowing exercise training of patients can reduce this risk.[75,76]

Functional aspects of the results of the Department of Veterans Affairs Laryngeal Cancer Study Group trial related to communication, swallowing and eating were reported by Hillman et al.[77] From the viewpoint of speech communication, patients treated with induction chemotherapy did better than those with removal of the larynx. For other non–speech-related measures, there were only a few significant differences between the 2 groups. Only 6% of patients undergoing total laryngectomy had development of usable esophageal speech, although the proportion of those who remained nonvocal was also small (8%). When assessing long-term quality of life in surviving patients from the Veterans' study, more favorable results were found in non-surgically treated patients. Better scores in various quality of life instruments appeared to be related to more freedom from pain, better emotional well-being, and lover levels of depression than to preservation of speech function.[78] Furthermore, Fung et al[79] reported on voice and swallowing outcomes of an organ preservation phase II trial for 97 patients with advanced laryngeal cancer. They were treated with a single course of PF induction chemotherapy followed by concurrent chemoradiation when the response was $\geq$50%, or with salvage laryngectomy when response was assessed to be less than 50%. Patients with an intact larynx demonstrated better voice-related quality of life than did patients treated with laryngectomy. Early salvage (immediately after unsuccessful induction chemotherapy) was associated with fewer surgical complications but no difference in voice-related outcome when compared with late laryngectomy (after chemoradiation failure). Although overall swallowing function was good in all patients, those with an intact larynx were more likely to obtain nutrition with oral intake alone without supplements.

Although the above mentioned developments and innovations have led to more intensive treatment approaches aimed at the best possible oncologic results, including laryngeal preservation rate, the morbidity connected to such treatment has increased accordingly. Probably the most important factors contributing to morbidity in these patients is dysphagia and aspiration as a consequence of radiotherapy to the larynx and pharynx. In this respect, relevant structures are the pharyngeal constrictors and supraglottic larynx.[80] More accurate delineation of target volumes may spare those critical structures. Intensity-modulated radiotherapy (IMRT) offers the possibility of reducing the volumes of these critical structures receiving high doses,[81] although in hypopharyngeal primaries in particular, growing next to or directly infiltrating structures important for intact swallowing function, such sparing effect of advanced irradiation techniques is less likely. Indeed, a prospective observational study showed that patients treated with IMRT had fewer swallowing problems after completion of radiotherapy or chemoradiation than patients treated with conventional three-dimensional conventional radiotherapy.[82] Most centers are also trying to spare high-dose radiation to one or more of the major salivary glands with these techniques, which has a beneficial effect on deglutition.[83]

Other recent developments are focused on reducing overlapping toxicity of concomitantly administered systemic agents and irradiation, specifically acute toxicity, lack of compliance and, consequently, late effects affecting function and quality of life. One of these developments is the use of biologic agents as radiosensitizers such as epidermal growth factor receptor inhibitors administered concurrently with either definitive radiotherapy or chemoradiotherapy regimens.[84] In a phase III randomized trial of radiotherapy and radiotherapy plus weekly doses of cetuximab, in patients with locoregionally advanced HNSCC, the 5-year overall survival rate was significantly improved with the addition of cetuximab, increasing from 36% to 46%, respectively.[85] In subgroup analysis, patients with oropharyngeal cancer seemed to benefit more than those with hypopharyngeal cancer, but the study was not powered for this additional analysis. There are no studies on the effectiveness of this treatment regimen in hypopharyngeal cancer in particular. So although potentially promising, possibly in combination with existing chemoradiotherapy regimens, the role of targeted systemic therapies in

the treatment of hypopharyngeal cancer remains to be established. Moreover, although intended to be less toxic, there may still be considerable side effects, particularly when used in combination with chemoradiotherapy.

Finally, in a study on quality of life of patients with HNSCC, no significant difference was found in overall health-related quality of life between patients treated with surgery followed by radiotherapy and patients treated with chemoradiation. The authors stated that because nonsurgical means of treating head and neck cancer have become more aggressive and surgical techniques have become more focused on function preservation and rehabilitation, the outcome from these 2 approaches is similar in terms of overall health-related quality of life.[86] In a long-term longitudinal study of quality of life, the presence of a feeding gastrostomy was found to be the variable most closely associated with poor quality of life.[87] This contrasts many surgeons' perception that the need for long-term tracheostomy or tracheostoma is the most serious functional sequel of treatment. However, the symbolic importance for the patients of keeping an intact larynx should not be underestimated. The French larynx preservation trial on induction chemotherapy conducted in the 1990s had to be closed prematurely because of strong patients' preference for the larynx preservation arm and insufficient accrual into the total laryngectomy arm.[88]

SALVAGE SURGERY

Although the focus of this article is on initial treatment, salvage surgery could be considered part of planned treatment by nonsurgical approaches. High rates of patient survival in larynx preservation trials are achieved because of effective salvage surgery for locoregional recurrences. The timing and means of surveillance and intervention are still a matter of debate,[89,90] but are undoubtably of importance. In the initial phase of the chemoradiation era planned neck dissections were the rule. Later it was realized that not all patients needed neck dissection. Conscientious surveillance and timely identification of those patients with resistant or recurrent disease for neck dissection made planned neck dissection obsolete.[91] Adequate and timely salvage surgery is important to obtain satisfactory locoregional control rates in cases of nonsurgical treatment strategies. 5-year local and regional control rates for salvage pharyngectomy have been reported in 71% and 70% of the cases, respectively.[92] However, less favorable results have also been reported. In a series reported by Relic et al,[93] only 2 of 20 patients undergoing surgery for histologically proven recurrence of laryngeal or hypopharyngeal cancer after chemoradiotherapy were tumor-free and alive after a mean observation time of 44 months.

Moreover, the rate of complications of surgery after chemoradiation has increased. For example, a high (up to 75%) rate of fistulas has been reported, depending on the interval between completion of radiotherapy and salvage surgery, and the dose of radiotherapy. Salvage surgery is associated with long-term stricture rates of 15%.[92,94–96]

CONCLUSIONS

Efforts to preserve speech and swallowing function in the treatment of hypopharyngeal (and laryngeal) cancer have resulted in a declining use of TLP. Surgical, as well as nonsurgical, options are available in an attempt to achieve these goals without losing the efficacy of treatment or ultimate tumor control and survival. However, when comparing data on survival, it should be kept in mind that the populations that have been treated with certain modalities are often selected and therefore comparison of results is difficult and should be done with caution (Table 1).[4,7,12,21,22,30,31,34–36,41–45,49,51–53]

With surgical approaches, PLP, as an open procedure or performed endoscopically as a less traumatic minimally invasive procedure, have offered the opportunity of preserving function of the larynx in selected cases of hypopharyngeal cancer. However, only selected cases will be suitable for this approach.

Many patients have benefited from the developments in nonsurgical treatment. A significant number of these patients retain their larynx, which otherwise would have been removed. The treatment is applicable to a wide spectrum of hypopharyngeal cancers, including intermediate-stage disease; only extensive disease with loss of function at presentation could best be treated with TLP as the primary option. However, although increasingly toxic chemoradiation protocols may further improve larynx preservation rates, this could be associated with significantly more pronounced toxicity and worse functional results. Developments aimed at improving results without increasing toxicity and morbidity are focused on technical improvements in radiotherapy, advances in supportive care and the use of new targeted therapy agents other than chemotherapeutics.

In early-stage disease, both surgery and radiotherapy are organ and function preserving treatment options. However, the role of surgery in early-stage hypopharyngeal cancer is less established than for laryngeal cancer. The choice of treatment may depend on patient-related factors like age, comorbidity,[97] occupation, patient preferences, and tumor-related factors such as size and localization. In advanced disease, most patients will be treated either with TLP followed by (chemo)radiotherapy or up-front chemoradiation. In selected cases partial surgery may be considered, but experience is greater with laryngeal cancer than with hypopharyngeal carcinoma, and favorable results can only be obtained in carefully selected patients and treatment by highly experienced teams.

Table 1. Survival rates of patients treated with different treatment modalities for hypopharyngeal cancer.

Treatment	No. of patients	Overall survival, 5 year (4 year) [3 year] {2 year}	Disease-specific survival, 5 year (4 year) [3 year]
TLP			
Kraus et al[4]	132	30%	41%
Frank et al[21]	110	18%*	—
		48%	—
Bova et al[22]	180	33%	52%
Ogura et al[30]	57	[36%]	—
Partial surgery			
Open procedures			
Ogura et al[30]	85	[59%]	—
Laccourreye et al[31]	34 (T2)	—	56%
Chevalier et al[34]	48 (T1/T2)	47%	—
		T1:78%	
		T2:38%	
Makeieff et al[35]	87 (T1/T2)	60%	—
		T1:83%	
		T2:50%	
Plouin-Gaudon et al[36]	34	50%	65%
Transoral procedures			
Steiner et al[41]	129	71% (stage I/II)	95% (stage I/II)
		47% (stage III/IV)	69% (stage III/IV)
Rudert and Höft[42]	29	48%	58%
Vilaseca et al[43]	28	(43%)	(59%)
Kutter et al[44]	58	{78%}	—
Martin et al[45]	172	68% (stage I/II)	96% (stage I/II)
		64% (stage III)	86% (stage III)
		41% (stage IV)	57% (stage IV)
Radiotherapy			
Gupta et al[7]	501	—	[41%]
Godballe et al[49]	101	16%	28%
Yoshimura et al[51]	77 (stage I/II)	47%	74%
Nakamura et al[52]	115 (stage I/II)	66%	77%
Rabbani et al[53]	123(stage I/II)	35%	61%
Chemoradiotherapy			
Lefebvre et al[12]	100	[57%]	[43%]
			25%

Abbreviation: TLP, Total laryngopharyngectomy.
**Without postoperative radiotherapy.*

When comparing nonsurgical and surgical treatment options, not only are traditional oncologic outcome measures important. Functional outcome and quality of life, in particular, are important as well. The latter studies are relatively scarce. Although chemoradiation has gained substantial popularity and seems to be an important treatment option at other sites of the head and neck, in hypopharyngeal cancer this is less obvious, both in terms of oncologic, as well as functional outcome. Lack of studies employing nonsurgical treatments exclusively in hypopharyngeal cancer precludes definitive conclusions.

The success of organ preservation protocols in laryngeal cancer has led to an increase in the use of primary chemoradiation in both laryngeal and extralaryngeal primary sites, despite a paucity of randomized clinical trial data comparing nonsurgical treatment to the "gold standard" of surgery followed by postoperative radiation for unfavorable pathologic features, and an increasing recognition that the high surgical salvage rates enjoyed by patients with laryngeal cancer do not necessarily translate to extralaryngeal sites. Therefore, despite the declining use of (open) surgery, the role of primary surgery in head and neck cancer should perhaps be reviewed.[98]

Although the emphasis has been shifted to nonsurgical treatments, these strategies still involve surgical procedures. Thus the role of the surgeon in treatment and follow-up remains important,[99] not only as an option for initial treatment, but also for salvage, tumor surveillance and the diagnosis and treatment of complications and functional impairments.

It is recognized that future studies need to be carefully designed with clearly defined populations and uniformity in terminology and endpoints.[15,69] Moreover, whereas most larynx preservation trials enroll patients with either laryngeal or hypopharyngeal cancer, it should be realized that these tumors are distinct entities. Results in laryngeal cancer may not directly translate to those in hypopharyngeal cancer. Therefore, specific trials for hypopharyngeal cancer would be needed.

It is plausible that selection is important in the choice of optimal treatment strategies. For surgical approaches to organ preservation, T classification, anatomic sublocalization, and extension of the primary tumor are more relevant selection criteria than the overall disease stage. In cases of nonsurgical treatment, volume of the primary tumor may be a predictive factor.[100] How other factors such as a patient's immune reactivity and the innate biology of an individual tumor relates to prognosis and therapy selection have yet to be explored. Most trials involving nonsurgical treatment strategies report on overall stage rather than T and N classification but stage may be a suboptimal criterion for selection of treatment. Small primaries classified as T1 and T2 but with extensive nodal metastases will be staged as IV and must be considered separately from large T4 tumors that are otherwise staged similarly.[101] A small primary tumor might very well be treated by partial surgery followed by postoperative radiotherapy when indicated. More extensive primary tumors will not be suitable for organ preserving surgery and may better be treated with chemoradiotherapy regimens with the intention of organ preservation. Very extensive primary tumors with extensive destruction and functional impairment of the larynx may be best treated with initial laryngopharyngectomy.

Thus, the clues to better oncologic, as well as functional, outcomes are probably to be found in appropriate patient selection. However, the optimal means for selection may be difficult to determine. Until more evidence is available to decide reliably about optimal treatment for the individual patient, each patient should be discussed by knowledgeable multidisciplinary teams weighing the many factors and options that influence an optimal and individualized treatment recommendation.

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